of missing data; and (3) ensure that a common set of *a priori* risk factors and effect modifiers are examined and treated according to consistent analytical criteria.

An analysis of the combined primary data from seven North American case–control studies (Connecticut/Utah/Idaho, Iowa, Missouri I and II, New Jersey I and II, and Winnipeg) was initiated at an international meeting of radon researchers in February 1995 sponsored by the U.S. Department of Energy and the Commission of European Communities (*4*). The decision to proceed with this analysis at that time followed a number of previous discussions on this initiative. Officials from Health Canada hosted a subsequent planning meeting in October 1995, including the principal investigators for all completed and ongoing North American case–control studies, other invited scientists with expertise in radon risk assessment, and representatives from the U.S. Department of Energy and the Commission of European Communities. At that meeting, all investigators agreed to submit their primary data according to a common format. After a subsequent planning meeting hosted by Health Canada in June 1997, the data available from the three completed North American case–control studies were included in a pilot analysis.[1] The three included studies were Missouri I, New Jersey I and Winnipeg, and involved a total of 1,590 cases and 2,215 controls.

The final data format for the pilot analysis included both static (age, year of case and control ascertainment, source of information, gender, active and passive smoking, education, family income, and ethnicity) and time-dependent variables (home sequence identifier, intensity of active smoking by the study subject and co-residents, radon concentration in the living area and basement, radon estimation method for the living area and basement, and proportion of time spent in the home). Prior to inferential analyses, these data were examined carefully to confirm correspondence with the originally published descriptive statistics. To obtain retrospective radon exposures for the period 5 through 50 years prior to enrollment into the study, missing measurements were imputed using the observed control mean as recommended by Weinberg *et al.* (*5*). A common logistic regression model involving both *a priori* and empirically chosen covariates was developed through parallel analyses of the three data sets. Modification of the radon effect by smoking, age at ascertainment, and gender was explored. The two-stage random-effects regression methods as described by Wang *et al.* (*6*) were then employed to derive an estimate of the combined overall radon effect. Sensitivity of the results to the definition of the time window of exposure and form of the statistical model were also investigated.

Preliminary results for three of the four ongoing studies were presented at the 1998 ASA Conference on Radiation and Health, and the extended abstracts appear in this volume (see abstracts by Field *et al.*, p. 101; Sandler *et al.*, p. 103; Alavanja *et al.*, p. 104). The Iowa case–control study includes extensive information on spatial variation of radon levels within residences and on radon exposures occurring outside the home. Restricting study subjects to people who had resided in the same home for at least 20 years minimized the need for imputation of radon values in this study. In addition to using current ambient radon measurements to predict historical radon exposures, both the Iowa study and Missouri II employed CR-39 α-particle track detectors affixed to selected household glass objects to estimate cumulative radon exposure more directly. All three studies included duplicate radon measurements in at least some homes, which will permit an assessment of exposure measurement error. Data from the four remaining studies, representing approximately 3,337 additional cases and 3,928 controls, were expected to be available for a complete analysis by the fall of 1998.

The North American pooling effort will be the largest study conducted to date of residential radon exposure and lung cancer, including some 4,927 cases and 6,143 controls. The available data will permit a more powerful examination of the critical exposure time window and potential modifiers of the association between residential radon and lung cancer than was possible in the pilot analysis, and will include additional factors previously unavailable, such as ventilation habits (sleeping with an open window in Utah/Idaho), activity-weighted particle size distribution, and equilibrium fraction (in Iowa). Following Darby *et al.* (*7*), attempts will be made to account for error in radon exposure estimation. It is anticipated that a preliminary analysis of the combined primary data will be the subject of the next meeting of the study participants in 1999.

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DISCUSSION: Indoor Radon and Risk of Lung Cancer

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Introduction

There have been eight case–control studies of residential radon and lung cancer published to date (*1*). Preliminary results have been presented at this conference on three studies (in Missouri, Iowa and Connecticut/Utah). In addition, results were presented at the 11th Annual Lectures on Radon, sponsored by the Institut für Strahlenschutz and held 18–19 March 1998 at the GSF-Forschungszentrum für Umwelt- und Gesundheit, Neuherberg, by S. Darby on a study in Cornwall and Devon in the United Kingdom (2) and by E. Wichmann on studies in the western and eastern parts of Germany. This brings to 14 the number of studies of indoor radon and lung cancer, with a total of 9,885 cases and 16,539 controls (Table 1). Except for the Cornwall/Devon study, the newer studies have not yet been published in peer-reviewed journals, and thus results should be considered preliminary.

The Connecticut/Utah study was presented at the ASA conference, but results were considered incomplete and are not included in Table 1 or in the following calculations.

Improvements in Study Design

The earliest studies of residential radon and lung cancer were targets of opportunity, with radon measurement protocols for houses added to ongoing lung cancer case–control studies. While the addition of measurement protocols to existing studies was not inherently limiting and did not necessarily result in biased estimates of relative risk (RR), the studies were not designed specifically to assess residential radon and so may have had limited coverage of the exposure time window, or may have

TABLE 1
Relative Risks (RR) and 95% Confidence Interval (CI) for Residential Radon Case-Control Studies

Study	RR[a]	95% CI	Cases	Controls
Finland I	1.30	1.1–1.6	164	334
Finland II[b]	1.26	1.1–1.6	517	517
New Jersey, U.S.	1.83	1.2–2.9	433	402
Shenyang, China	0.84	0.8–0.9	308	356
Winnipeg, Canada	0.96	0.9–1.1	698	738
Stockholm, Sweden	1.83	1.3–2.5	201	378
Sweden	1.20	1.1–1.3	1,281	2,576
Missouri I, U.S.	1.12	0.9–1.4	538	1,183
Missouri II, U.S.				
Surface[c]	2.29	1.7–3.1	372	471
Track-etch	0.78	0.6–1.0	247	299
Cornwall/Devon, UK	1.19	1.0–1.4	982	3,195
Western Germany[d]				
Total	1.04	0.9–1.3	1,449	2,297
Prone areas	2.66	2.0–3.5	365	595
Eastern Germany				
Total	1.16	1.0–1.4	1,053	1,667
Prone areas	1.40	1.0–1.9	NA[e]	NA
Iowa, U.S.	1.43	1.3–1.6	415	614
Connecticut/Utah	NA	NA	1,474	1,811
Total			9,885	16,539

[a] RR at 150 Bq m^{-3} based on a log-linear model, $RR(x) = \exp[\beta(x - x_0)]$, fitted to category-specific, adjusted RRs for each study, where x is the mean radon level and x_0 is the mean of the lowest category.

[b] RR estimate and 95% CI based on corrected data in erratum (*3*).

[c] Exposures estimated from CR-39 surface monitors or on track-etch air radon monitors.

[d] German results reported for complete data and for data restricted to radon-prone areas.

[e] Information not available.

collected fewer data on housing characteristics and other pertinent information. In addition, several of the earliest studies derived exposure estimates from radon measurements of 2 to 3 months duration, rather than 1 year, as in the more recent studies, or used short-term measurements of 1–2 weeks to supplement missing radon concentrations.

In contrast, the recent studies have included design elements that are associated with more complete and accurate radon measurement data and thereby more precise estimates of exposure (Table 2). Some of the important design elements are: more complete assessment of radon exposure by measuring all rooms of the house, as well as measuring outdoor radon levels; minimum residency restrictions for the current house, thereby limiting enrollment to subjects who were long-term residents; and use of surface radon detectors (CR-39 plastic on glass artifacts) that measure (average) radon concentration over many years. Improved study designs likely produced better-quality exposure data, although it cannot be known whether the studies that included some or all elements of Table 2 did in fact have more accurate exposure estimates.

Results of Studies and Summary Estimates from Meta-Analysis

As in Lubin and Boice (*1*), for each study we fitted the log-linear model, $RR(x) = \exp[\beta(x - x_0)]$, to the category-specific, adjusted RRs, where x is the mean radon level and x_0 is the mean of the lowest category. Table 1 shows estimates from the fitted model for 150 Bq m^{-3}, i.e. $\exp(\beta \times 150)$, for the previous eight studies (with the corrected Finland II data) and for the newest indoor radon studies.

For the newest studies, a significant exposure response for indoor radon was found for the Missouri II study when exposure estimates were based on CR-39 surface monitors, which were placed on glass artifacts and measured the long-term (average) radon concentration, but there was

TABLE 2
Improvements in Design of Recent Studies of Residential Radon and Lung Cancer

Restrictions on minimum residency time in current houses
Restrictions on the maximum number of houses lived in
Use of year-long radon detectors
Use of radon detectors that directly measure (average) exposure rates over many years
Increased efforts to measure or estimate radon exposure from all sources (e.g. all rooms of houses, outdoors, workplaces)
More complete information on residential occupancy, time spent indoors and within each room of house
More detailed information on housing characteristics and modifications
Use of unbiased methods for imputing missing radon data
Increased numbers of cases and controls
Increased power for analysis of smoking and radon exposure using randomized recruitment

no trend when exposure estimates were based on standard year-long track-etch detectors. The reason for this difference was unknown and was still being explored. A significant exposure–response relationship was found in the Iowa study.

The three studies presented at the Lectures on Radon in Germany showed mixed results. In the Cornwall/Devon study, RRs increased with increasing residential radon concentration (*2*). In this study, the investigators included a detailed evaluation of the impact of exposure misclassification on the estimate of trend in risk (*4*). The excess RR per Bq m^{-3} was increased about 50% after adjustment for measurement error. The studies in Germany were two of the largest studies and results depended on whether or not data were restricted. The exposure–response trends were statistically significant when data were limited to those areas defined as "radon prone". In the study in the eastern part of Germany, the exposure–response trend in the full data set was statistically significant, while the exposure–response trend in the restricted data was notably diminished in magnitude although still statistically significant. In the study in the western part of Germany, there was no significant exposure–response trend in the full data set. The reasons for different results based on data restrictions are as yet unexplained, but may have been related to patterns of exposure error.

Using data from the eight previously published radon studies, the estimated RR at 150 Bq m^{-3} based on log-linear models fitted to each of the studies and then combined into a summary trend was 1.18 with 95% CI (1.0, 1.4), indicating an overall significant risk of lung cancer from indoor radon. This estimate updates the RR estimate of 1.14 given by Lubin and Boice (*1*), who included the uncorrected Finland data. Based on the studies in Table 1, the summary estimate of the RR at 150 Bq m^{-3}, using results from the Missouri II study with exposure based on surface monitors and from the German studies with restricted data, was 1.35 with 95% CI (1.2, 1.5). The RR at 150 Bq m^{-3}, using results from the Missouri II study with exposure based on track-etch monitors and from the German studies without data restrictions, was 1.16 with 95% CI (1.0, 1.3).

As demonstrated in the report of the National Research Council's Committee (BEIR VI), the excess risks observed in the residential radon studies are consistent with predicted levels of risk from models developed from data on underground miners exposed to radon (*5*). In addition, the excess risks in the residential studies are consistent with RRs observed in miners with cumulative exposures similar to exposures experienced by long-term residents in high-radon houses.

Conclusion

The results from newest case–control studies of indoor radon continue to support the existence of a small excess lung cancer risk to the general population from residential radon. This excess is entirely consistent with extrapolations using models developed using data for miners.

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IV. DOSIMETRY AT LOW DOSE RATES

Chair: Richard W. Hornung, *University of Cincinnati*

Accounting for Bias and Measurement Error in Occupational Studies

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This work is motivated by the need to adjust for dose bias and uncertainty in epidemiological dose–response analyses. Typically, epidemiological studies of the effects of external penetrating radiation on worker health have relied on recorded annual doses to the individuals in the population. At Oak Ridge, these annual doses were obtained by adding up recorded weekly readings. In statistical analyses, these dose values have been treated as though they are known exactly, although everyone recognizes that there is uncertainty due to measurement error and bias. It is usually assumed that the measurement errors "average out" and that the bias is small. A recent study of Oak Ridge workers (*1*) used a preliminary dose adjustment procedure and found an upward bias in dose–response coefficients and likelihood ratio test statistics. This analysis was based on a crude adjustment for missing dose and did not consider measurement and other dosimetry errors.

Although our goal is to account for bias and uncertainty in occupational risk estimates for ionizing radiation, we find that the necessary first step is an adjustment for bias and quantification of uncertainty in dose estimates. So far, this is where most of our effort has been concentrated (*2, 3*). We describe our results in radiation dose estimation and comment on how the bias-corrected dose estimates that include quantification of uncertainty can be used in risk estimation.

Among occupational studies based on historical data, occupational radiation risk estimation is relatively "data rich". However, the data were collected for compliance rather than for estimation for individual doses. Consequently the bias can be substantial. Studies have shown that there was a systematic underestimation of doses for ORNL workers from 1945 to 1955 (*2, 3*). The first study (*2*) concentrated on dose estimation from film-badge data, and the second study (*3*) provided a systematic way of combining pocket-meter data with film-badge data for a better dose estimate. The results show that both bias and uncertainty vary widely between individuals and are poorly correlated with recorded annual dose. This suggests that the additional information contained in daily and weekly dosimetry records is needed for effective bias adjustment and quantification of uncertainty.

The dose estimate proposed for each individual is a probability distribution. This is the most general description of uncertainty and can be reduced to other descriptions of uncertainty. A nonparametric probability distribution estimate, consisting of many (say 100) density points, can be reduced to a more concise description such as the five points of a boxplot, or to a few parameters of an assumed parametric distribution (such as a normal or a lognormal distribution). Each reduction is a loss of information and a gain in simplicity. These can be computed for an individual or for any cohort of individuals. Such generality allows the dose estimates to be useful for many purposes, including adjustment for dose uncertainty in epidemiological dose–response analyses by methods yet to be developed.

Our methodology is based on Bayesian estimation of "true dose" from available dose measurements in the form of a probability distribution. Bayesian dose distributions from individual measurements are combined with convolution computations to obtain dose distribution estimates for longer periods.

The Bayesian statistical approach estimates the unobserved quantities (true doses) given the values of the observed ones (recorded doses). A relationship between the true dose and the recorded dose in the form of a conditional probability distribution is the key element of the method. We begin by defining $P(x)$ to be the true dose distribution that concerns one individual in one measurement period. The key component for implementing our approach is the conditional probability distribution $P(z|x)$. In effect, $P(z|x)$ is the answer to the question: "If the true dose is x, what is the probability that the recorded value is z?" This is determined by careful consideration of the properties of the measuring device (in this case the film badge or the pocket meter and the system used in reading and recording its dose). A necessary component is some information on the calibration error of the measuring device as well as recording practice. For the ORNL data, we assume a lognormal calibration error whose parameters are estimated from historical information. The rounding and censoring practices as well as use practices known from historical ORNL documents are included in the model of $P(z|x)$.

Note that $P(z|x)$ is a function of two variables, namely x and z, and it is constructed by specifying a distribution on z for each possible (fixed) value of x. After specifying $P(z|x)$ for all possible z and x, it is used as a function of x for each observed z. This is the "likelihood" of x for the observed z and is denoted by $L(x|z)$. Bayes's theorem then combines the likelihood $L(x|z)$ with prior distribution $P(x)$ to get $P(x|z)$, the posterior distribution of the true dose x given the recorded measurement z.

After the posterior dose distributions are obtained for each measurement period (in our case, a day or a week), the distributions must be "added" to compute a cumulative dose for a longer period. We compute yearly cumulative dose distributions, but other periods (such as a quarter to correspond to measurement periods in later years) may be used. Conditional on the recorded doses, the posterior distributions are independent and their convolutions can be computed efficiently with the discrete Fourier transform.

Because posterior distributions for individual measurements are often not symmetrical about the recorded measurement (in the ORNL case, especially the zero recorded doses), the cumulative distribution uncovers the bias in the added recorded doses.

When dose distributions for individuals are available, how can they be used in dose risk estimation? If we only wish to correct for bias in recorded doses, we can use the medians of the dose distributions and proceed with traditional dose–response analyses. Including dose uncertainty is more difficult. A Monte Carlo solution is possible but is also very computationally intensive. Other approaches that extend the dose estimation by Bayesian methodology into risk estimation can probably be developed. For example, some simple parametric assumptions about the dose distributions may carry through some known dose–response estimation methods. These may also require substantial computation, but less than the Monte Carlo solution.

A Monte Carlo simulation is more complex than it appears at first. The collection of risk estimates computed from samples generated by the individual dose distributions only accounts for the uncertainty in the data. We also need to account for error in the dose–response model. In traditional dose estimation, the model error is usually expressed by a confi-